REMARKS

Claims 22, 23, 24 and 28 have been amended. No new matter has been added. Support for the claim amendments may be found at, for example, the originally filed claims, p. 17, line 19, p. 27, lines 18-28 of the specification.

Claims 25-27 have been cancelled without prejudice. Applicants reserve the right to pursue the cancelled subject matter of those claims in a continuing application.

Claims 22-24 and 28 are currently pending.

SPECIFICATION

The Examiner has objected to the title of the invention and has kindly proposed a new title "A Method of Increasing the Amount of COX-1 mRNA in a Subject." See Office Action at p. 2. Applicants thank the Examiner for the proposed new title. The specification has been amended to include the Examiner's proposed new title.

CLAIM REJECTIONS

Rejection of claims under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 28 under 35 U.S.C. § 112, second paragraph, as being indefinite. See Office Action at p. 3. Specifically, the Examiner points to the phrase "a betaine replacement compound" and states that the "[i]t is unclear what compounds would be suitable for replacement of betaine ....." Id. Not in acquiescence but in an effort to expedite prosecution, Applicants have amended claim 28 clarify that that "a betaine replacement compound" is "any methyl donor." Accordingly, a person of skill in the art would be able to identify the metes and bounds of the claim. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of claims under 35 U.S.C. § 112, first paragraph

Enablement

The Examiner has rejected claim 27 under 35 U.S.C. § 112, first paragraph, for lack of enablement. See Office Action at p. 3. Not in acquiescence to the rejection, claim 27 has been cancelled thus rendering this rejection moot with respect to claim 27. Claim 22 however, has been amended to recite "wherein the microorganism is *Bifidobacterium* sp. 420."

With respect to *Bifidobacterium* sp. 420, the Examiner contends that "it is unclear if the

starting materials were readily available to the public at the time of invention." See Office Action at p. 3. The Examiner further notes that "[i]t appears that the species is available commercially at the time the application was filed, as noted on page 22 of the specification." See Office Action at p. 4. The Examiner also states that "it is not clear whether a deposit has been made and if the deposit meets all of the criteria set forth in 37 CFR 1.801-1.809." Id.

MPEP 2404.01 states that "[i]n an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public." Factors that can be used to determine that a biological material is known and readily available to the public include commercial availability. Id. The MPEP also states that "[t]he Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. Id.

Bifidobacterium sp. 420 is available commercially from Danisco A/S/ (Denmark) as indicated on p. 27, lines 19-20 of the specification. Applicants further include a Products and Services page from the Danisco website at Appendix A which states that *Bifidobacterium* is available to customers worldwide. Accordingly, *Bifidobacterium* sp. 420 is known and readily available to the public. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of claims under 35 U.S.C. § 102(b)

The Examiner has rejected claims 22-26 and 28 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent Publication No. 2002/0006432 to Collins ("Collins"). See Office Action at p. 5. Not in acquiescence to the rejection but in an effort to expedite prosecution, claims 25-26 have been cancelled thus rendering this rejection moot with respect to those claims. Claims 23-24 and 28 depend from independent claim 22.

With respect to claim 28, Applicants note that the Examiner states that Collins "does not specifically teach the addition of a betaine or a betaine replacement compound to the composition comprising the bacteria." See Office Action at p. 8. As such, Applicants submit that Collins does not anticipate claim 28 and respectfully request that this rejection be withdrawn with respect to claim 28.

Amended claim 22 relates to a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method

includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Collins describes isolated strains of probiotic bacteria and specifically, *Bigidobacterium longum infantis*. See paragraphs [0075]-[0076] of Collins. Collins does not teach a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Accordingly, claim 22 and dependent claims thereof are not anticipated by Collins. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of claims under 35 U.S.C. § 103(a)

Collins and Zimmer or Chen

The Examiner has rejected claims 22-26 and 28 under 35 U.S.C. § 103(a) as being unpatentable over Collins in view of U.S. Patent No. 5,501,857 to Zimmer ("Zimmer") or U.S. Patent Publication No. 2001/0014322 to Chen et al. ("Chen"). See Office Action at p. 7. Not in acquiescence to the rejection but in an effort to expedite prosecution, claims 25-26 have been cancelled thus rendering this rejection moot with respect to those claims. Claims 23-24 and 28 depend from independent claim 22.

Collins describes that

> [i]n vivo and in vitro studies were carried out using the probiotic bacteria strains. It was found that humans fed with yoghurt containing *Bifidobacterium longum infantis* UCC35624 show marked decreases in their systemic levels of IL-8. This strain may therefore have potential application in the treatment of a range of inflammatory disorders, particularly if used in combination with current anti-inflammatory therapies, such as non-steroid anti-inflammatory drugs (NSAIDs) or Infliximab.

See paragraph [0076] of Collins. Collins does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Collins further relates to the effects of a very specific *Bifidobacterium longum infantis*

UCC35624 strain on cytokine secretion by peripheral blood mononuclear cells. See for example, paragraphs [0142]-[0144] of Collins. In contrast, Applicants have surprisingly demonstrated that *Bifidobacterium* sp. 420 has direct effects on epithelial cell Cox gene expression. See Examples on p. 46-52 of the specification. Advantageously, this results in prevention of disease at an earlier stage before cytokine responses are induced. See for example, p. 2-3 of the specification. Therefore, conditions where alteration in epithelial Cox function is believed to be an early key step in the pathogenesis (such as side effects associated with nonsteriodal anti-inflammatory drugs) can be more efficiently inhibited by the method described in claim 22.

Further, a person of skill in the art would not be motivated to substitute the specific *Bifidobacterium longum infantis* UCC35624 strain used in Collins for another strain of *Bifidobacterium* since the disclosure of Collins is restricted to a very specific *Bifidobacterium longum infantis* UCC35624 strain and to the advantages that that strain has. Collins does not teach or suggest substituting *Bifidobacterium longum infantis* UCC35624 strain with another strain of *Bifidobacterium*, let alone *Bifidobacterium* sp. 420.

Such defects are not remedied by Zimmer. Zimmer describes an "oral nutritional supplement, i.e., a dietary adjunct, for livestock which includes incompatible live microbial cultures, and vitamin and mineral supplements, each separated from the other via multiple encapsulation." See Abstract of Zimmer. In Example 10 of Zimmer, "[t]he microorganisms are a formulation of commercially available dormant *Bifidobacterium longum*." Zimmer does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-l mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Chen describes a microbe composition that includes "a symbiotic mixture of three lactic acid producing bacteria consisting of *Bifidobacterium bifidum* 6-1, *Lactobacillus acidophilus* YIT 2004 and *Streptococcus faecalis* YIT 0027." See paragraph [0025] of Chen. Chen states that

> [i]t is the object of the present invention to provide a microbe composition which: (1) exerts a control mechanism for the micro ecological balance between enteric microbes and their human host; (2) is antagonistic to pathogens and/or potential pathogens such as Salmonella, Shigella, *E. coli* and V. *cholerae*, especially when

the pathogens and/or potential pathogens are resistant to various antibiotics; (3) is effective in treating various kinds and degrees of diarrhea; (4) stimulates peristaltic movement of the intestinal tract which not only prevents toxic microbial colonization and eliminates noxious microbial products but also alleviates constipation; (5) enhances immunologic function of the human host; (6) is effective in decreasing the levels of endotoxin and abnormally elevated cytokine IL-6 in the blood of the human host; (7) is effective in improving and enhancing liver function; (8) is effective in treating acute and chronic hepatitis in active stage especially when it is accompanied with endotoximia; (9) is effective in alleviating liver cirrhosis; (10) is non-toxic and has no side effects and (11) is stable, convenient to store and use.

See paragraph [022] of Chen. Chen does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-l mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420. A person of skill in the art would not be motivated to combine Collins with Chen as Chen does not teach or suggest that *Bifidobacterium* sp. 420 increases the amount of COX-1 mRNA in at least one cell of the subject.

None of the above-mentioned references, alone or in combination, teach or suggest teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-l mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Since claims 23-24 and 28 depend from independent claim 22, those claims should be patentable over the combination of Collins and Zimmer or Chen for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Collins and Van Der Mei

The Examiner has rejected claims 22-27 under 35 U.S.C. § 103(a) as being unpatentable over Collins in view of Van Der Mei, *J. Med. Microbiol.,* Vol. 49, p. 713-718 (2000) ("Van Der Mei"). See Office Action at p. 9. Not in acquiescence to the rejection but in an effort to expedite prosecution, claim 25-27 have been cancelled thus rendering this rejection moot with

respect to those claims. Claims 23-24 depend from independent claim 22.

As previously explained, Collins does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-l mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Independent claim 22 relates to a method which increases the level of COX-1 mRNA in at least one cell of a subject. As mentioned above, a person of ordinary skill in the art seeking a solution to the problem of how to increase COX-1 mRNA would not be motivated to look to Collins because Collins is silent on how to increase COX-1 mRNA. Even if a person of skill in the art were to seek to follow the teachings of Collins, such a person would not extrapolate the teachings in Collins regarding the specific strain *Bifidobacterium longum infantis* with any other *Bifidobacterium* species, let alone with *Bifidobacterium* sp. 420.

The Examiner acknowledges that Collins "does not specifically teach the use of *Bifidobacterium* sp. 420 in the method of using the bacteria" (see Office Action at p. 9) but contends that Van Der Mei corrects such deficiencies because Van Der Mei describes that "*Bifidobacterium* sp. 420 was an available species of bacteria" and "that the species may have probiotic effects." See Office Action at p. 10. Applicants respectfully traverse this analysis by the Examiner.

Firstly, there is no indication in either Collins or Van Der Mei that *Bifidobacterium* sp. 420 may be able to increase COX-1 mRNA. Secondly, there is not even a suggestion in either Collins or Van Der Mei that *Bifidobacterium* sp. 420 could be utilized in the method of Collins. In addition, Van Der Mei describes the effects of probiotic bacteria on the prevalence of yeasts in oropharyngeal biofilms on silicone rubber voice protheses. See abstract. This is a completely different field of use for the bacteria component compared to their effects on cytokine secretion by peripheral blood mononuclear cells described in Collins. There are no teachings either in Collins or in Van Der Mei which indicate that a bacteria which affects the prevalence of yeasts in oropharyngeal biofilms on silicone rubber voice protheses would have effects on cytokine secretion by peripheral blood mononuclear cells. Thus a person of ordinary skill in the art would have no motivation to combine the teaching of Collins and Van Der Mei.

Applicants further submit that at the filing date of the above-mentioned application, there were a huge number of *Bifidobacterium* strains available. Of all the strains available, there is

nothing to motivate a person of skill in the art to pick and use *Bifidobacterium* sp. 420 in the method of Collins and substitute the very specific *Bifidobacterium longum infantis* strain described in Collins. Van Der Mei does not remedy such a deficiency. Van Der Mei is not a review of different *Bifidobacterium* which may have probiotic effects. There is no indication in Van Der Mei that *Bifidobacterium* sp. 420 has advantages over any other strain of *Bifidobacterium*, let alone that it would be advantageous in the method of Collins. In fact, Van Der Mei found *Bifidobacterium* sp. 420 to not be particularly effective (see Abstract, "Exposure of oropharyngeal biofilms on voice prostheses to suspensions of *Bifidobacterium* sp. 420 or *Enterococcus faecium* 603 did not significantly reduce the number of yeasts in the biofilm. However, suspensions of *Lactobacillus fermentum* B54, *L. rhamnosus* 744 or *L. lactis cremoris* Sk11 led to a reduction in the number of yeasts harvested from voice prostheses."). Thus, it can be seen that Van Der Mei actually teaches away from using *Bifidobacterium* sp. 420.

In view of the above, in the absence of hindsight analysis, it can be seen that there is no motivation for a person of skill in the art to use *Bifidobacterium* sp. 420 in the method of Collins.

Since claims 23-24 depend from independent claim 22, those claims should be patentable over the combination of Collins and Van Der Mei for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

CONCLUSION

Applicant believes that the claims are in condition for allowance. A petition for a two-month extension of time is attached.

Should any fees be required by the present Reply, the Commissioner is hereby authorized to charge Deposit Account 19-4293.

Respectfully submitted,

Date: 3-29-10

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APPENDIX A

← back to Products & Services
← back to Product range

CULTURES
- Dairy cultures
- Meat ripening cultures
- Probiotic cultures
- Protective cultures

- Competencies
- Events

Text size: A A

Cultures

Cultures are blends of natural microorganisms or strains with a history of safe use. Largely comprising lactic acid bacteria, cultures also cover other types of bacteria as well as yeasts and moulds.

Danisco's cultures have been specifically screened, selected and formulated to achieve defined characteristics in terms of robustness throughout production process and functionalities in food products throughout shelf life.

Danisco's comprehensive range of cultures include
- Lactic starters
- Probiotic cultures for the health and nutrition market
- Ripening and flavouring cultures for cheese
- Maturation and surface ripening cultures for meat products
- Protective cultures
- Fermentates

Application areas

Our cultures have been tested for a wide range of fermented or non-fermented applications. They are available as Direct Vat Inoculation or DVI cultures that are ready to be inoculated without scale up at the processor plant or as Bulk Set cultures for the following markets:
- cheese: fresh cheese, soft cheese, semi and hard , probiotic cheese etc.
- fresh fermented milks: yogurts, probiotic daily doses, kefir, elben, quark, sour cream, buttermilk etc.
- beverages: probiotic fruit juices & smoothies
- confectionery, such as nutrition bars or chocolate confectionery
- dried and semi-dried sausages: salami, summer sausage, chorizo, pepperoni, fuet etc.
- dried cured meat: dry hams, bacon etc.
- cooked hams
- fresh ground meats: chipolatas, merguez, Bratwurst etc.
- culinary applications such as prepared foods, ready to eat meals, soups etc.
- dietary supplements
- nutritionals such as energy bars, infant or toddler formulas

Functionalities

Cultures are widely use in the food industry to preserve microbiological qualities as well as develop organoleptic features such as texture, colour and taste. In addition, human clinical studies have demonstrated the health benefits of specific probiotic strains that are today widely used and recognised to enhance digestive health and immune system modulation.

Danisco's ability to control the characteristics of the strains and to formulate them makes it possible to obtain end products with highly defined properties.

Microorganisms	Functionalities	Food applications
Lactic Acid Bacteria (LAB) Main genera: - Streptococcus - Lactococcus - Leuconostoc - Enterococcus - Pediococcus - Lactobacillus - Bifidobacterium	Acidification Texturising Flavouring Colouring Inhibiting properties Health benefit	Dairy (fresh fermented, yoghurts, cheeses) Dietary supplements Meat products Beverages Nutritionals
Moulds Main genera: - Penicillium - Geotrichum	Colouring Flavouring Surface protection	Dairy (cheeses) Meat products
Yeasts Main genera: - Geotrichum - Candida - Kluyveromyces	Colouring Flavouring Surface protection	Dairy (cheeses) Meat products

Innovation
Read more about our competencies within cultures

Want to know more about Danisco's Cultures division?

Danisco focuses on
- Health & Nutrition
- Food protection

- Debaryomyces - Rhodosporium		
Other bacteria Propionibacteria and surface bacteria - Corynebacteria - Micrococacceae	Gas production Colouring Flavouring	Dairy (cheeses) Meat products
Fermentates Cultured skim milk	Growth control of spoilage organisms	Dairy Meat products Culinary products

Culture availability

Based on their production process and the location of their plant facilities, our customers worldwide can choose between freeze-dried, frozen or liquid format.

News

Danisco Cultures doubles its freeze-drying capacity	22 Feb 2010
Boost your immune defences with HOWARU® probiotic juices	21 Jan 2010
Danisco at the forefront of phage-resistant bacteria research	8 Jan 2010
Danisco A/S signs agreement to acquire Sorbial	11 Nov 2009
HOWARU® Probiotic Yogurt Bears	10 Nov 2009

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